PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SJKBP6224695	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/002408	International filing date *(day/month/year)* 07.06.2004	Priority date *(day/month/year)* 09.06.2003
International Patent Classification (IPC) or national classification and IPC A61K47/48		
Applicant CONSEJO SUPERIOR DE INVESTIGACIONES CIENTIFICAS		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.06.2005	16.09.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Gonzalez Ramon, N Telephone No. +31 70 340-3466

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/002408

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-48 as originally filed

Claims, Numbers

1-65 as originally filed

Drawings, Sheets

1/8-8/8 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/002408

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-15, 20-36, 40-46, 49, 51-56, 58, 60-65 in part; 16-19, 37-39, 47, 48, 50, 57, 59 complete

because:

☒ the said international application, or the said claims Nos. 60-65 in relation to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-15, 20-36, 40-46, 49, 51-56, 58, 60-65 in part;16-19, 37-39, 47, 48, 50, 57, 59 complete

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/002408

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 12, 13 complete 1-11, 14, 15, 20-36, 40-46, 49, 51-56, 58, 60-65 in part .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6-10, 41-43, 46, 51
	No:	Claims	1-5,11-15,20-36,40,44,45,49,52-56,58,60-65
Inventive step (IS)	Yes:	Claims	41-43, 46, 51
	No:	Claims	1-15,20-36,40, 44,45,49,52-56,58,60-65
Industrial applicability (IA)	Yes:	Claims	see separate sheet
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 60-65 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

In the present application, the International Searching Authority has restricted the search under the following objections under Articles 5 and 6 PCT.

The use of the term "about" (claims 6, 7) in reference to a range is unclear (Art 6 PCT).

Claims 1-15, 20-36, 40-46, 49, 51-56, 58, 60-65 as far as related to the first invention encompass a genus of compounds defined only by their function, namely "a ligand" (claims 1, 20, 29, 36, 52, 59-61); "an NMR active atom" (claims 14, 22); "a label" (claim 21); "pharmaceutically active component" (claim 25); "ligand capable of binding a receptor on a cell" (claim 26), "a linker" (claim 53); "a candidate compound" (claim 60); "a substance capable of binding to a ligand) (claim 61); "species suspected to interact via carbohydrate mediated interaction" (claim 64) wherein the relationship between the structural features of the members of the genus and said function has not been defined.

In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition.

The fact that one could have assayed a compound of interest using the described assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound **(other than those that might be particularly disclosed in the application)** would fall within the scope of what is claimed.

It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.

Moreover the use of said terms as "a ligand"; "an NMR active atom"; "a label"; "pharmaceutically active component"; "ligand capable of binding a receptor on a cell", "a linker"; "a substance capable of binding to a ligand"; "species suspected to interact via carbohydrate mediated interaction" would encompass not yet described or prophetical

compounds and would therefore contravene Art. 5 PCT.

Therefore, claims 1-15, 20-36, 40-46, 49, 51-56, 58, 60-65 do not fulfil the requirements of Art. 5 and Art. 6 PCT.

Moreover present claims 1-15, 20-36, 40-46, 49, 51-56, 58, 60-65 relate to compounds/methods defined by reference to vague characteristics or properties, namely: "metal atom", (claim 1); "passive metal" (claims 2, 3); "magnetic metal atoms" (claim 2); "fluorescent group", "radioactive isotope" (claim 22); "a peptide" (claim 23); "DNA or RNA" (claim 24); "a condition ameliorated by the administration of the ligand" (claim 34); "that would otherwise cause a pathology" (claim 35); "an antibody" (claim 63).

Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed.

Support with regard to the first invention above is only to be found in the present application for those parts relating to the compounds/methods explicitly disclosed in the examples and those specifically mentioned by chemical name in claims 4, 5, 8, 11-13, 15, 20, 31, 32, 40-46, 49, 51, 54-56, 65.

No opinion will be formulated by the ISA in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT)

Re Item IV
Lack of unity of invention

The applicant was informed that the search is the responsibility of the ISA under Chapter I of the PCT, the procedure before the ISA is closed and that there is no provision in the PCT for a review of or an appeal against the findings of the ISA, either by the ISA itself or by the IPEA.

An international search report **has only been established for the subject matter of invention 1 as listed below.**

No international Preliminary Examination will be carried out in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT) (I. e. inventions 2-9 as listed)

1. Claims 12, 13 complete 1-11, 14, 15, 20-36, 40-46, 49, 51-56, 58, 60-65 in part

Magnetic nanoparticle of less than 2.5 nm diameter having a core of metal atoms wherein the core is covalently linked to a plurality of ligands wherein the ligand incorporates a

lanthanide. Excluding the subject matter of inventions 2-9

2. Claims 16, 17, 47, 48, 57, 59 complete; 1-11, 14, 15, 20-36, 40-46, 49-56, 58, 60-65 in part
Magnetic nanoparticle of less than 2.5 nm diameter having a core of metal atoms wherein the core is covalently linked to a plurality of ligands wherein the ligand comprises a carbohydrate group (polysaccharide, oligosaccharide, monosaccharide). Excluding the subject matter of inventions 1, 3-9.

3. Claims 18, 19 complete; 1-11, 14, 15, 20-36, 40-46, 49, 51-56, 58,60-65 in part

Magnetic nanoparticle of less than 2.5 nm diameter having a core of metal atoms wherein the core is covalently linked to a plurality of ligands wherein the ligand comprises a glycanoconjugate (glycolipid or glycoprotein). Excluding the subject matter of inventions 1, 2, 4-9.

4. Claims 1-11, 14, 15, 20-37, 39 in part

Use of a magnetic nanoparticle of less than 2.5 nm diameter having a core of metal atoms wherein the core is covalently linked to a plurality of ligands wherein the ligand comprises an antigen for the preparation of a medicament for vaccinating. Excluding the subject matter of inventions 1-3, 5-9.

5. Claims 38 complete; 1-11, 14, 15, 20-37, 39 in part

Use of a magnetic nanoparticle of less than 2.5 nm diameter having a core of metal atoms wherein the core is covalently linked to a plurality of ligands wherein the ligand comprises a nucleic acid encoding an antigen for the preparation of a medicament for vaccinating. Excluding the subject matter of inventions 1-4, 6-9.

6. Claims 1-11, 14, 15, 20-36, 40-46, 49, 50 in part

Use of a magnetic nanoparticle of less than 2.5 nm diameter having a core of metal atoms wherein the core is covalently linked to a plurality of ligands wherein the ligand comprises a hormone or DHEA for the preparation of a medicament for treatment of cancer metastasis. Excluding the subject matter of inventions 1-5, 7-9.

7. Claims 1-11, 14, 15, 20-36, 40-46, 49, 50 in part

Use of a magnetic nanoparticle of less than 2.5 nm diameter having a core of metal atoms

wherein the core is covalently linked to a plurality of ligands wherein the ligand comprises a peptide capable of binding to a cell-specific receptor for the preparation of a medicament for treatment of cancer metastasis. Excluding the subject matter of inventions 1-6, 8, 9.

8. Claims 1-11, 14, 15, 20-36, 40-46, 49, 50 in part
Use of a magnetic nanoparticle of less than 2.5 nm diameter having a core of metal atoms wherein the core is covalently linked to a plurality of ligands wherein the ligand comprises a lipid for binding a toll receptor for the preparation of a medicament for treatment of cancer metastasis. Excluding the subject matter of inventions 1-7, 9.

9. Claims 1-11, 14, 15, 20-36, 40-46, 49, 50 in part

Use of a magnetic nanoparticle of less than 2.5 nm diameter having a core of metal atoms wherein the core is covalently linked to a plurality of ligands wherein the ligand comprises methylene blue for the preparation of a medicament for treatment of cancer metastasis. Excluding the subject matter of inventions 1-8.

Re Item V
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

For the assessment of the present claims 60-65 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The applicant's attention is drawn to the fact that the present opinion expressed as to novelty, inventive step and industrial applicability refers only to matter for which an international search report has been drawn up.

No international Preliminary Examination will be carried out in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT)

Reference is made to the following documents:

D1: WO 99/61911 A (HOSTETLER MICHAEL J ; TEMPLETON ALLEN C (US); UNIV NORTH CAROLINA (US)) 2 December 1999.
D2: WO 02/32404 A (MARTIN LOMAS MANUEL ; ROJO JAVIER (ES); PENADES

SOLEDAD (ES); CONSEJO) 25 April 2002

D3: TERANISHI T. ET AL: GOLD, 2003, pages 978-982.

D4: SRIKANTH H. ET AL: MATERIALS SCIENCE AND ENGINEERING, vol. 304-306, 2001, pages 901-904.

D5: PARK S.J. ET AL: J. AM. CHEM. SOC., vol. 122, 2000, pages 8581-8582.

Novelty Article 33(2) PCT

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-5, 11-15, 20-36, 40, 44, 45, 49, 52-56, 58, 60-65 is not new in the sense of Article 33(2) PCT.

D1 discloses nanometer sized (1-7 nm preferred, see page 6, paragraph 2) with a core including gold, silver, copper, palladium, platinum, nickel or alloys thereof and a reactive substituent monolayer to be modified with a functional material (metal ligand, chromophore, fluorophore, nucleotides, aminoacids, sugars) (see page 10, paragraph 2; claims 6, 8, 9, 11).
Link to the core include element-sulfur bond to the core and thioester bond to the functional material (see page 8, paragraph 3- page 9, paragraph 1).
Despite the applicant's argumentation, the particles discloses are effectively tested under nuclear magnetic resonance technique (see examples), and therefore implicitly and unequivocally magnetic particles
Consequently the subject matter of present claims 1-5, 11, 20-22, 25-28, 30-33, 40, 52, 53, 58 is not novel in view of D1.

D2 discloses magnetic nanoparticles comprising a metal core selected from Au, Ag, Cu and their alloys and a plurality of ligands (carbohydrate groups alone or in combination with peptides, protein domains, nucleic acid segments or fluorescent groups) (see page 5, paragraph 2; claims 1, 4-6, 12-16, 18-23, 25-35, 39).
The ligand is derivatised as a protected disulfide and coupled to the particles (see page 8, paragraph 3). Mean particle diameter is 1.8 nm (see page 28, paragraph 2; figure 2).
Despite the applicant's argumentation, the particles disclosed comprise core which is NMR active and are detected by nuclear magnetic resonance technique (see claims 5, 6, 34), and therefore unequivocally encompass magnetic particles.

Consequently the subject matter of claims 1, 3-5, 11-15, 20-36, 40, 44, 45, 49, 52-56, 58, 60-65 is not new over D2.

D3 describes alkanetriol-protected Au nanoparticles in the range from 1.5 to 9.7 nm. The ligand 2,6-bis(1'-(n-thioalkyl)benzimidazol-2-yl) pyridine (namely BIP group) is serving as a tridentate ligand (see abstract, page 980, figure 4).

Therefore the subject matter of present claims 1, 3-5, 11, 14, 15, 20-22, 28, 31, 32, 40, 52-54, 58 is not novel over D3

Inventive step Article 33(3) PCT

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-15, 20-36, 40, 44, 45, 49, 52-56, 58, 60-65does not involve an inventive step in the sense of Article 33(3) PCT.

The problem underlying the present invention is the preparation of magnetic nanoparticles bound to ligands suitable for medical use by a synthetic method allowing to achieve stable and desired sized nanoparticles (page 5, lines 8-12).

As solution to this problem a magnetic nanoparticle of less than 2.5 nm diameter having a core of metal atoms wherein the core is covalently linked to a plurality of ligands wherein the ligand incorporates a lanthanide, as well as their preparation methods and uses are proposed as the first invention.

Document D2, which can be considered the closest prior art, already addresses the problem of preparation of magnetic nanoparticles of metal core (Au, Ag, Cu and their alloys) bound to ligands suitable for medical use by a synthetic method to achieve stable nanoparticles of a diameter of less than 2.5 nm (see page 28, paragraph 2, figure 2)

The difference between D2 and the subject matter of the present application is the fact that the particular combination of passive metal atoms (gold, platinum, silver or copper) with magnetic metal atoms (iron, cobalt, gadolinium) forming part of the core of the particle is not explicitly disclosed in D2.

The skilled man, would have easily contemplated the use of the combination of Au-Fe of the nanoparticles described in D4, comprising a 3nm Au core (see figure 1) as suitable core material for the preparation of nanoparticles described by D2.

D5 discloses the synthesis and magnetic studies of uniform iron nanorods and nanospheres.

It is further obvious for the skilled person to routinely tune synthetic modifications in the method of preparation as taught by D2 (see page 28) or D5 (see page 8581, col. 2) in order to obtain precisely sized nanoparticles of less than 2.5 nm as the claimed by the present application.

Consequently the subject matter of present claims 1-15, 20-36, 40, 44, 45, 49, 52-56, 58,

60-65 cannot be considered as involving an inventive step.